Title: Pregnancy outcomes following maternal venlafaxine use; a prospective observational comparative cohort study

Running Title: Safety of venlafaxine use in human pregnancy

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ABSTRACT

Background: Venlafaxine is a serotonin noradrenaline reuptake inhibitor used to treat major depressive episodes and anxiety disorders. The primary aim of this study was to investigate spontaneous abortion risks following gestational exposure.

Methods: This prospective observational comparative cohort study utilised data collected by the UK Teratology Information Service (UKTIS) between 1995 and 2018. The study sample included 281 venlafaxine exposed pregnancies matched to antidepressant unexposed (n=1,405) and SSRI exposed (n=843) comparator groups.

Results: After correction for variation in competing outcome rates and the stage of pregnancy at reporting, no statistically significant differences in the hazard of spontaneous abortion was observed following gestational venlafaxine use compared with either antidepressant unexposed (HR 1.28, 95%CI; 0.850 to 1.94) or SSRI exposed (HR 1.03, 95%CI; 0.681 to 1.57) pregnancies.

Conclusions: No conclusive evidence is provided from this study that venlafaxine increases the risk of adverse pregnancy or fetal outcomes.

HIGHLIGHTS

- The primary aim of this study was to investigate spontaneous abortion risks following gestational venlafaxine use
- No statistically significant differences in the hazard of spontaneous abortion was observed following gestational venlafaxine use compared with either antidepressant unexposed (HR 1.28, 95%CI; 0.850 to 1.94) or SSRI exposed (HR 1.03, 95%CI; 0.681 to 1.57) pregnancies
- Secondary aims were to investigate congenital malformation and other adverse pregnancy outcome risks
- The overall rate of major congenital malformation among the venlafaxine-exposed group (1.42%), was not significantly different from the antidepressant-unexposed (1.36%) and SSRI-exposed (1.67%) comparator groups
- No statistically significant differences in preterm birth or fetal growth parameters were observed
- The findings of this study therefore provide no conclusive evidence that venlafaxine is a major human teratogen or fetotoxic agent

1. INTRODUCTION

Maternal depression is common during pregnancy, with published estimates ranging from 4 to 20%.[1] Consequently gestational antidepressant use is frequent and has increased over recent decades in Europe[2] and the United States.[3] Adequate treatment is important becausepoorly controlled gestational depression may increase the risk of adverse maternal[4, 5] fetal,[6] and childhood developmental outcomes.[7, 8] It is therefore essential that adequate pregnancy pharmacovigilance data are available to allow informed discussions about the safety of gestational medication use between patients and health professionals.

Venlafaxine is a serotonin noradrenaline reuptake inhibitor (SNRI) licensed for the treatment and prevention of major depressive episodes, the treatment of generalised and social anxiety disorder, and treatment of panic disorder with or without agoraphobia.[9]

There are considerable human pregnancy exposure data available, which together does not provide evidence that venlafaxine increases the overall rate of congenital malformation.[10-15] However, less data are available concerning risks of specific malformations and outcomes such as spontaneous abortion,[16-18] intrauterine fetal death/stillbirth,[19] preterm delivery[16] and low birth weight.[16] The primary aim of this study was to increase the amount of published data available concerning the risk of spontaneous abortion following venlafaxine exposure in pregnancy. Secondary aims were to investigate intrauterine fetal death/stillbirth, preterm delivery, fetal growth restriction and congenital malformation risks**.**

2. MATERIALS AND METHODS

2.1 Study design, setting and data collection procedures

This study utilised a prospective observational comparative cohort design to analyse teratogen surveillance data collected by the UK Teratology Information Service (UKTIS) using standardised procedures. In brief, UK-based healthcare professionals are encouraged to contact UKTIS to discuss the potential fetal effects of maternal environmental exposures (medicines/occupational chemicals etc.) during pregnancy. Upon contact with the service, relevant clinical, obstetric and demographic patient information is collected from the health professional to allow accurate fetal risk assessment. Subsequently, all enquiries which involve maternal exposures in pregnancy are included in the prospective surveillance system. This system utilises postal questionnaires sent shortly after the estimated date of delivery (EDD) to collect pregnancy and fetal outcome data from the healthcare professional who originally contacted the service.

2.2 Study sample

This study sample consists of non-duplicate pregnancy/fetal outcomes collected by the service following reports of maternal exposures between September 1995 and August 2018. All pregnancies where maternal age details were unavailable, multiple pregnancies (twins/triplets), or where maternal poisonings, overdoses or exposure to known or suspected human teratogens/fetotoxic agents (including any retinoid, cytotoxic or antiepileptic medication, lithium, methotrexate, mycophenolate mofetil, thalidomide, warfarin or coumarin derivatives) was reported (with the exception of alcohol and tobacco) were excluded.

The exposed study group included pregnancies in which mothers had used venlafaxine at any stage of pregnancy. This was compared with two SNRI unexposed comparator groups matched to the venlafaxine exposed pregnancies by both calendar year and and maternal age (each ±2 years) at UKTIS referral. To provide standard reference outcome rates from the UKTIS surveillance system, the primary matched comparator group consisted of pregnancies unexposed to any antidepressant medications (matching ratio 5:1). These pregnancies were typically reported to UKTIS to discuss exposure to agents not known to be teratogenic such as vitamin supplements, dental x-rays mild and simple analgesics such as paracetamol or acetylsalicylic acid. To control by design for the potential impact of confounding variables common to women with gestational depression, a disease-matched comparator group was included which consisted of matched SSRI antidepressant exposed pregnancies (matching ratio 3:1). These disease-matched comparators were selected by SSRI exposure status and the health professional reported exposure indication only. No information was available to UKTIS regarding disease type or severity.

2.3 Definitions

Standard definitions for the exposure and outcome variables were used for this study, further details are provided in Table 1 of the Supplementary Appendix.

2.4 Statistical analysis

Normality of continuous variables was assessed using the Shapiro-Wilks test. Continuous variables which were not considered normally distributed were described using the median and interquartile

range and compared using the Mann-Whitney-Wilcoxon test. Categorical variables were expressed as counts and percentages, and were compared using Chi-squared or Fisher's exact tests when Chi-squared assumptions were not met. Rates of pregnancy and fetal outcomes were compared between exposed and control groups using exact methods to generate unadjusted crude odds ratios (OR) and their 95% confidence intervals. Additional adjusted analyses were conducted using binomial logistic regression to assess the impact of co-variates (tobacco, alcohol, recreational drug and folic acid use) on adverse pregnancy outcome risk estimates. In instances where these exposures were not confirmed by the reporting healthcare professional, non-exposure was assumed.

Crude spontaneous abortion rates were calculated for pregnancies reported to UKTIS prior to 24 weeks which did not result in elective termination. For the venlafaxine and SSRI exposed pregnancies the respective exposures must also have been prior to 24 weeks. Crude intrauterine fetal death/stillbirth rates were calculated using pregnancies which resulted in either an intrauterine fetal death/stillbirth or live birth as the rate denominator. Crude congenital malformation rates were calculated for all reported pregnancies after excluding those which resulted in congenital malformations considered as genetic/cytogenetic in aetiology.

To account for variation in both the stage of pregnancy at reporting to UKTIS and rates of competing risks, event-history analysis methods[20] were used to compute the cumulative incidence of spontaneous abortion and compare these between the exposed and comparator groups. This analysis was conducted using a restricted dataset of pregnancies where the maternal stage of pregnancy was reported at the initial time of reporting to UKTIS and when the pregnancy ended, and provided venlafaxine/SSRI use occurred during the risk period (<24 weeks gestation). Cause-specific cumulative incidences and their 95% confidence limits were plotted and compared using a Z-test.[20] Time-dependent Cox proportional hazards models were also constructed to compare the hazard of spontaneous abortion between the exposed and comparator groups whilst accounting for the impact of competing risks and left-truncation. Variables entered into the unadjusted models included the stage of pregnancy (in weeks post-LMP) at reporting to UKTIS and separately at pregnancy outcome, the venlafaxine exposure status, and the pregnancy outcome (elective termination, spontaneous abortion, stillbirth or live birth). Proportional hazards assumptions were tested using Schoenfeld residuals and a chi-squared test to identify non-proportionality (P<0.05). The impact of co-variates (history of spontaneous abortion and exposure to tobacco, alcohol, recreational drugs and folic acid) were also estimated by adding these details to the Cox proportional hazards models.

All data manipulations and statistical analyses were conducted in R version 3.4.1.[21] Matching of venlafaxine and comparator pregnancies was undertaken using the "Optmatch"[22] package in R. Logistic regression analyses were conducted using the "aod"[23] add-on packages. Event-history analysis methods and the Cox proportional hazards models were performed using the "ETM"[24] and "Survival"[25] add-on packages. No multiple comparison corrections were performed, and a *P*-value of <0.05 was used to indicate statistical significance in all tests.

2.5 Regulatory and ethical considerations

Regulatory approval for the national surveillance conducted by UKTIS is provided through section 251 of the NHS Act 2006. The analysis of routine anonymised surveillance data collected through this mechanism did not require separate approval by a UK Research Ethics Committee.

3. RESULTS

3.1 Study sample

A total of 7,897 pregnancies did not meet any of the study exclusion criteria, from which 281 venlafaxine exposed pregnancies were identified and matched to 1,405 antidepressant unexposed pregnancies and 843 SSRI exposed pregnancies.

Gestational venlafaxine exposure occurred in at least the first trimester for the majority of the venlafaxine exposed study group (n=270/281, 96.1%), with treatment being initiated before the 24th gestational week of pregnancy in all but four. Details relating to the exact gestational age (in weeks post-LMP) when venlafaxine treatment was started were available for 196 pregnancies. Of these, the majority were exposed from prior to conception (n=167/196, 85.2%), and for exposures where venlafaxine was commenced during pregnancy (n=29), therapy was started at a median of 6 weeks (IQR: 5 to 10 weeks, range 3 to 21). A total of 174 pregnancies had information relating to the stage of pregnancy when venlafaxine was both commenced and ended, and these data describe a median therapeutic exposure period spanning 7 gestational weeks (IQR: 5 to 11 weeks, range 1 to 40)

Concomitant psychiatric medication use was common among the venlafaxine exposed pregnancies with co-exposure to other antidepressants, antipsychotics, benzodiazepines or hypnotic benzodiazepine receptor antagonists being reported for 94 of 281 women in this group (33.5%). In the SSRI exposed group comparator group, 79 women used more than one SSRI, with the majority were exposed to fluoxetine (33.0%), citalopram (31.2%) or sertraline (21.4%), with fewer exposed to paroxetine (16.6%), escitalopram (3.08%) and fluvoxamine (0.237%).

3.2 Maternal demographics

A comparison of the maternal demographics among the three study groups is provided in Table 1. The matching process limited any statistically significant differences between the exposed and comparator groups for both calendar year of pregnancy and maternal age. In comparison with the antidepressant unexposed pregnancies those exposed to venlafaxine were reported to UKTIS at a significantly earlier stage of pregnancy, the median BMI was significantly higher (although there was no overall significant difference when maternal BMI was compared categorically), and a significantly higher proportion reported gestational tobacco use. In contrast, comparisons with the SSRI exposed controls did not identify any statistically significant differences.

Table 1: Comparison of maternal demographics between the venlafaxine, antidepressant unexposed and SSRI exposed study groups

	Venlafaxine	Antidepressant Unexposed	P-Value	SSRI	P-Value
Total Participants - n	281	1,405	-	843	-
Year of TIS Reporting - data available n (% total)*	281 (100)	1,405 (100)	-	843 (100)	-
Enrolment year - median (IQR)	2006 (2001 to 2012)	2007 (2001 to 2012)	0.907	2007 (2002 to 2012)	0.856
Maternal Age at TIS Reporting - data available n (% total)*	281 (100)	1,405 (100)	-	843 (100)	-
Age - median (IQR)	31 (28 to 35)	31 (28 to 35)	0.974	31 (27 to 35)	0.936
<20 or ≥35 - n (%)	85 (30.2)	423 (30.1)	1.00	247 (28.1)	0.821
GA at TIS Reporting - data available n (% total)	249 (88.6)	1,281 (91.2)	-	750 (89.0)	-
Weeks post-LMP - median (IQR)	7 (5 to 11)	***10 (6 to 20)***	***<0.001***	8 (5 to 15)	0.0722
Ethnicity - data available n (% total)	76 (27.1)	350 (24.9)	-	200 (23.7)	-
White ethnicity - n (%)	71 (93.4)	***291 (83.1)***	***0.0213‡***	181 (90.5)	0.633
BMI - data available n (% total)	56 (19.9)	268 (19.1)	-	147 (17.4)	-
BMI Score (kg/m^2) - median (IQR)	28.0 (23.1 to 32.8)	***25.0 (22.2 to 29.0)***	***0.0334***	25.8 (22.3 to 32.3)	0.309
Underweight (< 18.5 kg/m^2) - n (%)	3 (5.36)	8 (2.99)	0.0645‡	4 (2.72)	0.316‡
Healthy (18.5 to 24.9 kg/m^2) - n (%)	18 (32.1)	125 (46.6)		66 (44.9)	
Overweight (25.0 to 29.9 kg/m^2) - n (%)	14 (25.0)	73(27.2)		29 (19.7)	
Obese (≥ 30 kg/m^2) - n (%)	21 (37.5)	62 (23.1)		48 (32.7)	
Gravidity - data available n (% total)	236 (84.0)	1,119 (79.6)	-	698 (82.8)	-
Multi-gravida - n (%)	163 (69.1)	727 (65.0)	0.259	482 (69.1)	1.00
History of SA - n (% multi-gravida)	26 (16.0)	105 (14.4)	0.712	53 (11.0)	0.429
Tobacco Use - data available n (% total)	100 (35.6)	509 (36.2)	-	295 (35.0)	-
Use in pregnancy - n (%)	51 (51.0)	***197 (38.7)***	***0.0295***	157 (53.2)	0.788
Alcohol Use - data available n (% total)	62 (22.1)	246 (17.5)	-	148 (17.6)	-
Use in pregnancy - n (%)	22 (35.5)	91 (37.0)	0.942	59 (40.0)	0.660
Recreational Drug Use - data available n (% total)	74 (26.3)	339 (24.1)	-	198 (23.5)	-
Use in pregnancy - n (%)	11 (14.9)	49 (14.5)	1.00	29 (14.7)	1.00
Folate Use - data available n (% total)	78 (27.8)	438 (31.2)	-	246 (29.2)	-
Use in pregnancy - n (%)	73 (93.6)	415 (94.8)	0.595‡	228 (92.7)	1.00‡

Key: SSRI= selective serotonin reuptake inhibitors, TIS= teratology information service, IQR= interquartile range, GA= gestational age, BMI= body mass index, * indicates matched demographics, ‡ indicates that the *P*-value was calculated using Fisher's exact test

3.3 Pregnancy and fetal outcomes

Comparisons of the crude pregnancy/fetal outcome rates are provided in Table 2. There were limited differences in adverse pregnancy/fetal outcomes among the three groups. In comparison with the antidepressant unexposed controls, the crude rate of live birth was significantly decreased following venlafaxine exposure; an observation which appeared mainly driven by a statistically significant increase in crude spontaneous abortion rate. However, when comparisons were made with the disease-matched SSRI-exposed group, no statistically significant differences were observed for any of the outcomes analysed.

Table 2: Comparison of crude pregnancy and fetal outcome rates between the venlafaxine, antidepressant unexposed and SSRI exposed study groups

	Venlafaxine	Antidepressant Unexposed	P-Value	OR (95% CI)	SSRI	P-Value	OR (95% CI)
Total Pregnancies	281	1,405	-	-	843	-	-
ETOP - n (%)	21 (7.47)	103 (7.33)	1.00	1.02 (0.595 to 1.68)	71 (8.42)	0.706	0.878 (0.502 to 1.48)
SA - n (%*)	46 (21.0)	140 (14.5)	0.0225	***1.57 (1.06 to 2.30)***	114 (20.1)	0.865	1.05 (0.700 to 1.57)
IUFD/SB - n (%**)	3 (1.40)	12 (1.03)	0.717‡	1.36 (0.245 to 5.11)	7 (1.06)	0.714‡	1.32 (0.219 to 5.85)
LB - n (%)	211 (75.1)	1150 (81.9)	0.0111	***0.669 (0.490 to 0.919)***	651 (77.2)	0.515	0.889 (0.643 to 1.24)
GAD recorded	198	1,081	-	-	614	-	-
PTD - n (%)	33 (16.7)	125 (11.6)	0.0589	1.53 (0.974 to 2.35)	81 (13.2)	0.269	1.32 (0.819 to 2.08)
Infants with GAD & BW recorded	140	815	-	-	460	-	-
Term LBW - n (%)	4 (2.86)	29 (3.56)	0.807‡	0.797 (0.200 to 2.32)	22 (4.78)	0.477‡	0.586 (0.144 to 1.77)
SGA - n (%***)	12 (9.02)	65 (9.00)	1.00	1.00 (0.478 to 1.94)	55 (12.6)	0.339	0.691 (0.326 to 1.36)
Genetic Conditions Excluded	281	1,400	-	-	838	-	-
Any CM - n (%)	7 (2.49)	47 (3.36)	0.579‡	0.736 (0.278 to 1.66)	33 (3.94)	0.353‡	0.623 (0.230 to 1.45)
Major CM - n (%)	4 (1.42)	19 (1.36)	1.00‡	1.05 (0.258 to 3.19)	14 (1.67)	1.00‡	0.850 (0.202 to 2.74)
Minor CM - n (%)	3 (1.07)	28 (2.00)	0.463‡	0.529 (0.102 to 1.73)	19 (2.27)	0.319‡	0.465 (0.0876 to 1.60)
T1 Exposed	270	1,400	-	-	716	-	-
Any CM - n (%)	7 (2.59)	47 (3.36)	0.706‡	0.766 (0.289 to 1.73)	28 (3.90)	0.440‡	0.654 (0.238 to 1.56)
Major CM - n (%)	4 (1.48)	19 (1.36)	0.779‡	1.09 (0.268 to 3.32)	12 (1.68)	1.00‡	0.882 (0.206 to 2.94)

Key: OR= odds ratio, CI= confidence interval, SSRI= selective serotonin reuptake inhibitors, ETOP= elective termination of pregnancy, SA= spontaneous abortion (*denominator restricted to exclude pregnancies ending in ETOP or reported to UKTIS ≥24 weeks gestational age - venlafaxine n=219, antidepressant unexposed n=965 and SSRI n=566), IUFD/SB= intrauterine fetal death or stillbirth (**denominator restricted to exclude pregnancies ending in ETOP or SA - venlafaxine n=214, antidepressant unexposed n=1,162 and SSRI n=658), LB= live birth, GAD= gestational age at delivery, PTD= preterm delivery, BW= birth weight, LBW= low birth weight, SGA= small for gestational age (***denominator restricted to exclude pregnancies without relevant information for calculating the SGA rate - venlafaxine n=133, antidepressant unexposed n=722 and SSRI n=438), CM= congenital malformation, T1= first trimester

‡ indicates that the *P*-value was calculated using Fisher's exact test

3.3.1 Spontaneous abortion risks

To assess the risk of spontaneous abortion whilst controlling for variation in the stage of pregnancy reporting to UKTIS and rates of competing risks, event-history analysis was performed on a restricted dataset (venlafaxine n=208, NTE n=912 and SSRI n=550). Crude analysis of this restricted dataset produced similar risk estimates to those presented in Table 2 (data presented in supplementary table 2), although a lower rate of elective termination was observed following venlafaxine exposure in comparison with the antidepressant unexposed group.

Figure 1 provides plots of the event-history analysis adjusted spontaneous abortion cumulative incidences for the venlafaxine exposed pregnancies (24.5, 95% CI; 17.0 to 34.6) in comparison with (a) the antidepressant unexposed (20.3, 95% CI; 16.2 to 25.1) and (b) the SSRI exposed comparator groups (28.2, 95% CI; 21.4 to 36.7). As demonstrated by the overlapping plots of cumulative incidence functions, after adjustment for variation in gestational age at enrolment and competing risks no statistically significant differences remained (Z-test P=0.198 and P=0.264 respectively). Unadjusted time-dependent Cox proportional hazards models comparing the casue-specific hazard of spontaneous abortion between the venlafaxine exposed and a) the antidepressant unexposed (HR 1.28, 95% CI; 0.85 to 1.94) and (b) the SSRI exposed comparator groups (HR 1.03, 95% CI; 0.681 to 1.57) also provided no evidence of an association.

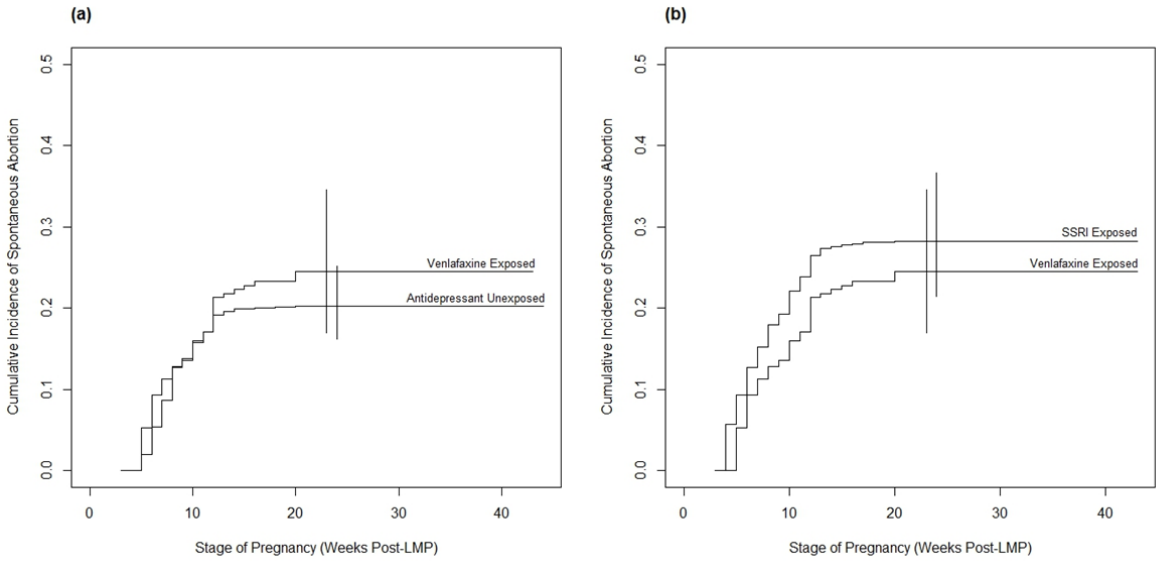

Figure 1: Comparison of the cumulative incidence of spontaneous abortion between venlafaxine exposed and the (a) antidepressant unexposed (P=0.198) and (b) SSRI exposed study groups (P=0.264).

3.3.2 Congenital malformations

Seven venlafaxine exposed infants were reported to have congenital malformations, Four infants with major malformations including tetralogy of Fallot, fixed bilateral talipes equinovarus, hypospadias, and meningoencephalocele diagnosed via ultrasound scan with subsequent elective termination, each affecting a single infant exposed in the first trimester. Three minor malformations

included one infant with unilateral mild talipes equinovarus and a capillary haemangioma, one infant with a funnel chest and one male infant with unilateral cryptorchidism.

Comparisons of the crude malformation rates are provided in Table 2. There were no statistically significant differences in major malformation rates following exposure at either any time in pregnancy or following exposure in the first trimester only.

3.3.3 Adjusted analyses

Adding co-variable estimates to the cause-specific Cox proportional hazards models did not have a substantial effect on the risk estimate or the statistical significance for the hazard of spontaneous abortion following venlafaxine exposure in comparison with either the antidepressant unexposed (aHR 1.26, 95% CI; 0.829 to 1.91) or SSRI-exposed controls (aHR 1.00, 95% CI; 0.655 to 1.53).

Similarly, consideration of co-variable estimates did not alter the statistical significance for the risks of preterm delivery, term low birth weight, small for gestational age, any or major congenital malformation, including with restriction to first trimester exposed pregnancies (Table 3).

Table 3: Comparison of pregnancy and fetal outcome rates between the venlafaxine, and the antidepressant unexposed and SSRI exposed study groups whilst also considering estimates of co-variables

	Venlafaxine	**Antidepressant Unexposed**	**aOR (95% CI)**	**SSRI**	**aOR (95% CI)**
GAD recorded	198	1081	-	614	-
PTD - n (%)	33 (16.7)	125 (11.6)	1.51 (0.979 to 2.27)	81 (13.2)	1.32 (0.844 to 2.06)
Term Infants with BW recorded	140	815		460	
Term LBW - n (%)	4 (2.86)	29/ (3.56)	0.794 (0.231 to 2.08)	22/ (4.78)	0.610 (0.175 to 1.64)
SGA - n (%*)	12 (9.02)	65 (9.00)	1.03 (0.508 to 1.89)	55 (12.6)	0.714 (0.353 1.35)
Genetic Conditions Excluded	281	1400		838	
Any CM - n (%)	7 (2.49)	47 (3.36)	0.711 (0.290 to 1.50)	33 (3.94)	0.641 (0.257 to 1.39)
Major CM - n (%)	4 (1.42)	19 (1.36)	1.06 (0.305 to 2.87)**	14 (1.67)	0.864 (0.243 to 2.44)
T1 Exposed	270	1400		716	
Any CM - n (%)	7 (2.59)	47 (3.36)	0.628 (0.238 to 1.38)	28 (3.90)	0.567 (0.209 to 1.30)
Major CM - n (%)	4 (1.48)	19 (1.36)	1.10 (0.316 to 2.97)**	12 (1.68)	0.893 (0.247 to 2.60)

Key: aOR= adjusted odds ratio, CI= confidence interval, SSRI= selective serotonin reuptake inhibitors, GAD= gestational age at delivery, PTD= preterm delivery, BW= birth weight, LBW= low birth weight, SGA= small for gestational age (*denominator further restricted to exclude pregnancies without relevant information for calculating the SGA rate - venlafaxine n=133, antidepressant unexposed n=722 and SSRI n=438), CM= congenital malformation, T1= first trimester
Odds ratios adjusted for tobacco, alcohol, recreational drug and folic acid use

4. DISCUSSION

Comparisons between the venlafaxine-exposed and the antidepressant unexposed group identified a statistically significant increased crude rate of spontaneous abortion, but this was not observed in comparison with a disease-matched control group of SSRI exposed pregnancies. Furthermore, event-history analysis adjustment and inclusion of the data in a time-dependent Cox proportional hazards model which both account for variation in gestational age at enrolment and rates of competing risks attenuated the statistically significant difference. No statistically significant differences in preterm birth or fetal growth parameters were observed. The overall rate of major congenital malformation among the venlafaxine-exposed group (1.42%), was not significantly different from the antidepressant-unexposed (1.36%) and SSRI-exposed (1.67%) comparator groups. As such, the findings of this study provide no conclusive evidence that venlafaxine is a major human teratogen or fetotoxic agent.

4.1 Published evidence

Controlled studies investigating the risk of adverse pregnancy or fetal outcomes following maternal venlafaxine use in human pregnancy consist of eight prospective cohort studies,[10-13, 15-17, 26] four case-control studies[18, 27-29] and a systematic review[14] which together report the outcomes of at least 4,000 unique exposed pregnancies. None of these studies have identified statistically significant increased risks of any congenital malformation overall,[10-16] however, some conflicting results have been provided for other adverse pregnancy/fetal outcomes.[17, 18, 27, 29] Two studies suggested possible associations with spontaneous abortion,[17, 18] while one did not.[16] Two case-control studies which used an overlapping dataset also suggested possible associations with cardiac malformation,[27, 29] but other large cohort studies have not replicated these findings.[10, 12, 13, 15] Associations with other specific malformations have also been reported in individual studies[10, 27-29] including cleft palate,[27, 29] gastroschisis,[27, 29] limb defects,[27] anencephaly,[29] hypospadias,[28] and respiratory system defects.[10]

4.2 Interpretation of study results

As the results of this prospective comparative cohort study suggest that the differences in crude spontaneous abortion rates observed between the venlafaxine exposed and antidepressant unexposed study group may have been due to data confounding, and no statistically significant increased risks of other adverse pregnancy or fetal outcomes were observed, the findings are considered to be largely in keeping with the published literature.

4.3 Strengths and limitations

This study represents the first controlled analysis of maternal venlafaxine use using surveillance data collected from a UK pregnant population. To limit the impact of inclusion bias, the surveillance data included in this study were collected prospectively. Both comparator groups were sourced internally using the same data collection procedure as for the venlafaxine exposed study group. This is also the largest disease-matched controlled study to investigate congenital malformation risks following maternal venlafaxine use in pregnancy. The disease-matched comparator group of SSRI exposed pregnancies was included to assess possible confounding by indication. Observations of similar adverse pregnancy/fetal risk estimates for the venlafaxine and SSRI exposed groups (see Table 2)

could be indicative of data confounding, highlighting the importance of a disease-matched control group and subsequently allowing more accurate conclusions to be drawn from the results. Alternatively however, it is accepted that given the disease-matched control group used in this study was not unexposed to medication, these results could have been produced due to similar fetal effects of both SSRI and venlafaxine intrauterine exposure.

The predominant limitation of the UKTIS surveillance method relates to the potential for adverse outcome detection heterogeneity. As UKTIS collect outcome information from numerous healthcare professionals, responder clinical knowledge and experience is not standardised which could theoretically lead to variation in the rate of outcome reporting. Additionally, outcome data are requested shortly following the estimated delivery date, but these outcome information may be provided up to six months post-delivery. As evidence is available which has shown that a higher proportion of infants are diagnosed with congenital malformations by one year of age than at birth,[30] non-standardisation of the time at which outcomes are provided may represent an additional source of outcome reporting variation.

In relation to the analysis of the spontaneous abortion data, adequate details regarding the exact stage of pregnancy when venlafaxine exposure began and ended was not available for a large proportion of the exposed pregnancies. It was therefore not possible to undertake an analysis which considered venlafaxine exposure as a time-dependent variable.

A further important limitation was the small sample size which precluded the ability to detect increased risks for some of the adverse pregnancy outcomes analysed. For example, with a major congenital malformation rate of 1.36% among the antidepressant unexposed pregnancies (matched 5:1), the venlafaxine exposed study sample size (n=281) was only sufficient (statistical power 80% and alpha 0.05) to detect an approximate 3.4-fold increased risk. As a result some imprecise risk estimates were provided. There were also a small number of pregnancies with exposure to venlafaxine in monotherapy. The ability to use statistical techniques to adjust risk estimates for concomitant exposures and variation in maternal demographics was limited by the large amount of missing data present in the UKTIS dataset. As such, it was only possible to add estimates of binary co-variables to the statistical models. These included maternal exposure to tobacco, alcohol, recreational drugs and folic acid during pregnancy, and were categorised as dichotomous variables (exposure yes or no), with absent values interpreted as no exposure. Other more detailed variables, such as those relating to body mass index, ethnicity or gravidity, could not be considered. Furthermore, the magnitude of the missing data, which exceeded 10% for most variables, precluded the reliable use of multiple imputation techniques.[31] Residual data confounding is therefore likely, however, restricting the venlafaxine and SSRI exposed groups by excluding all pregnancies where the mothers used more than one class of psychiatric medication did not substantially alter the results presented in Table 2 (data presented in supplementary table 4).

5. CONCLUSIONS

No conclusive evidence of an increased risk of adverse pregnancy or fetal outcomes is provided from this study of gestational venlafaxine use. However, further research may be warranted.

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7. SUPPLEMENTARY TABLES

Table S1: Exposure and outcome variable definitions

Variable	Definition
Gestational age	Estimated from ultrasound examinations or in weeks post the first day of the last menstrual period (LMP) when ultrasound examinations had not been performed
First trimester	First 13 weeks of pregnancy (0 to 90 days post-LMP)
Spontaneous abortion	Fetal loss up to 24 completed weeks gestation (up to 168 days post-LMP)
Intrauterine death/stillbirth	Fetal loss from 24 weeks onwards (169+ days post-LMP) or peripartum death
Body mass index (BMI)	Calculated as kg/m^2, underweight <18.5, normal range 18.5-25, overweight 25-30, and obese ≥30
Preterm delivery	Live born infants delivered prior to 37 completed weeks
Low birth weight	Live born infants with a birth weight <2,500g
Small for gestational age	Defined as a live born infant with a birth weight for gestational age which was less than the 10^{th} percentile after consideration of the infant sex and maternal parity
Birth defects	Birth defects reported to the service which were not considered to be of genetic aetiology were classified as either major or minor as per the EUROCAT classification system. Classification was performed by two of the study authors (AG and LMY) whilst blind to maternal exposure status. In cases of disagreement, consensus was achieved through discussion.

Table S2: Comparison of crude outcome rates between the venlafaxine, and the antidepressant unexposed and SSRI exposed study groups after restriction to include pregnancies reported to UKTIS prior to 24 weeks gestational age where the gestational age at pregnancy outcome was also available

	Venlafaxine	Antidepressant Unexposed	OR (95% CI)	SSRI	OR (95% CI)
Total Pregnancies	208	912	-	550	-
ETOP - n (%)	8 (3.85)	40 (4.39)	0.872 (0.347 to 1.93)	29 (5.27)	0.719 (0.279 to 1.65)
SA - n (%*)	31 (14.9)	83 (9.10)	***1.75 (1.08 to 2.77)***	77 (14.0)	1.08 (0.661 to 1.72)
IUFD/SB - n (%**)	3 (1.44)	7 (7.68)	1.89 (0.313 to 8.37)	6 (1.09)	1.33 (0.213 to 6.28)
LB - n (%)	166 (79.8)	782 (85.8)	***0.657 (0.441 to 0.993)***	438 (79.6)	1.01 (0.67 to 1.54)

Key: OR= odds ratio, CI= confidence interval, SSRI= selective serotonin reuptake inhibitors, ETOP= elective termination of pregnancy, SA= spontaneous abortion (*denominator restricted to exclude pregnancies ending in ETOP reported to UKTIS ≥24 weeks gestational age - venlafaxine n=212, antidepressant unexposed n=925 and SSRI n=583), IUFD/SB= intrauterine fetal death or stillbirth (**denominator restricted to exclude pregnancies ending in ETOP or SA - venlafaxine n=171, antidepressant unexposed n=802 and SSRI n=450), LB= live birth

Table S3: Comparison of crude pregnancy and fetal outcome rates between the venlafaxine, and the antidepressant unexposed and SSRI exposed study groups after exclusion of pregnancies where the mothers used more than one class of psychiatric medication

	Venlafaxine	**Antidepressant Unexposed**	**OR (95% CI)**	**SSRI**	**OR (95% CI)**
Total Pregnancies	187	1382	-	674	-
ETOP - n (%)	15 (8.02)	102 (7.38)	1.09 (0.577 to 1.95)	61 (9.05)	0.877 (0.451 to 1.61)
SA - n (%*)	36 (23.8)	137 (14.3)	***1.59 (1.02 to 2.42)***	90 (19.2)	1.11 (0.699 to 1.74)
IUFD/SB - n (%**)	3 (2.21)	11 (0.962)	2.32 (0.41 to 8.93)	5 (0.956)	2.33 (0.358 to 12.2)
LB - n (%)	133 (71.1)	1132 (81.9)	***0.544 (0.382 to 0.784)***	518 (76.9)	0.742 (0.509 to 1.09)
GAD recorded	126	1,063	-	488	-
PTD - n (%)	20 (15.9)	121 (11.4)	1.47 (0.831 to 2.49)	59 (12.1)	1.37 (0.748 to 2.43)
Term Infants with BW recorded	92	802	-	373	-
Term LBW - n (%)	2 (2.17)	26 (3.24)	0.664 (0.0751 to 2.72)	14 (3.75)	0.57 (0.0618 to 2.55)
SGA - n (%***)	7 (8.05)	62 (8.71)	0.917 (0.342 to 2.1)	37 (10.6)	0.267 (1.76 to 0.556)
Genetic Conditions Excluded	187	1,377	-	669	-
Any CM - n (%)	3 (1.6)	47 (3.41)	0.462 (0.091 to 1.46)	24 (3.59)	0.439 (0.0836 to 1.47)
Major CM - n (%)	2 (1.07)	19 (1.38)	0.773 (0.0866 to 3.25)	11 (1.64)	0.647 (0.0691 to 3)
Minor CM - n (%)	1 (0.535)	28 (2.03)	0.259 (0.00631 to 1.59)	13 (1.94)	0.272 (0.00635 to 1.83)
T1 Exposed	183	1,377	-	583	-
Any CM - n (%)	3 (1.64)	47 (3.41)	0.472 (0.093 to 1.49)	20 (3.43)	0.47 (0.0883 to 1.61)
Major CM - n (%)	2 (1.09)	19 (1.38)	0.790 (0.0885 to 3.32)	9 (1.54)	0.705 (0.0735 to 3.45)

Key: OR= odds ratio, CI= confidence interval, SSRI= selective serotonin reuptake inhibitors, ETOP= elective termination of pregnancy, SA= spontaneous abortion (*denominator restricted to exclude pregnancies ending in ETOP reported to UKTIS ≥24 weeks gestational age - venlafaxine n=151, antidepressant unexposed n=960 and SSRI n=468), IUFD/SB= intrauterine fetal death or stillbirth (**denominator restricted to exclude pregnancies ending in ETOP or SA - venlafaxine n=136, antidepressant unexposed n=1,143 and SSRI n=523), LB= live birth, GAD= gestational age at delivery, PTD= preterm delivery, BW= birth weight, LBW= low birth weight, SGA= small for gestational age (***denominator restricted to exclude pregnancies without relevant information for calculating the SGA rate - venlafaxine n=87, antidepressant unexposed n=712 and SSRI n=348), CM= congenital malformation, T1= first trimester